suggesting that this method could be used *in vivo* to enhance gene therapy. The Office Action further states that because those of skill in the art would be motivated to enhance gene therapy, it would have been obvious to combine the teachings of Dyer with those of Hodgson *in vivo*, because Dyer teaches a method of enhancing transfection of HSV-1 using dextran sulfate and that HSV-1 is capable of infecting a variety of cell types in different animals. Applicants respectfully disagree with the maintenance of this rejection, as neither Hodgson nor Dyer suggest or provide motivation to use viruses in *in vivo* methods, as is required by the present claims.

The context in which Hodgson teaches the use of viral vectors is set forth in the first two sentences of the abstract of the paper, where a contrast is made between the use of retrovirus-derived vectors and transfection in *ex vivo* gene therapy methods. In particular, Hodgson notes that retrovirus-derived particles are preferred for use in *ex vivo* gene therapy methods, due to their permanent (yet inefficient) integration into host DNA. Hodgson then goes on to note the increased efficiency of transient transfection methods (e.g., the use of cationic lipids), and the remainder of the paper focuses on the application of approaches similar to those used in transfection (e.g., the use of liposomes) to enhance the efficiency of retroviral transduction. These approaches are discussed only in the context of *ex vivo* gene therapy and, consistent with this, all of the experiments described in the paper are *in vitro*. There simply is no suggestion or motivation to introduce viruses into cells *in vivo* from Hodgson, as was stated in the Office Action.

Motivation to carry out *in vivo* methods is also not provided by the Dyer paper. The focus of this paper is the study of cell surface components involved in the entry of herpes simplex viruses (HSV) into cells. This study was facilitated by the use of a mutant cell line, sog9, which does not synthesize glycosaminoglycans. Using these cells and exogenously added

glycosaminoglycan analogs, such as dextran sulfate, the authors were able to show directly that cell surface glycosaminoglycans provide a matrix for virus adsorption onto cells, and that the mechanisms by which HSV-1 and HSV-2 enter cells can differ. Dyer concludes the paper by stating that it will be interesting to expand these findings by identifying and characterizing the domains of a herpes virus glycoprotein (gB) that mediate the differential binding. Dyer further concludes that the differences in adsorption and entry of HSV-1 and HSV-2 may be involved in the different epidemiologies of the viruses (page 197, first column). Dyer makes no mention of using glycosaminoglycans *in vivo*. Rather, these compounds were simply used by Dyer as tools to investigate mechanisms of viral entry into cells. Dyer, thus, is a basic research paper that simply does not provide any *in vivo* teachings or motivation.

Thus, neither Hodgson nor Dyer provides any suggestion or motivation to carry out viral administration *in vivo*, as is required by the present claims. Whether or not Hodgson and Dyer would provide any expectation that such an approach would work *in vivo* (which applicants submit that they would not, even if considered in the context of a suggestion for use in *in vivo* methods, which has not been provided in this rejection; see applicants' previous reply) is not really relevant to the fundamental problem with this rejection, which is that there is no suggestion or motivation in Hodgson or Dyer to carry out any methods *in vivo*, let alone those of the present claims.

This motivation also does not come from the other references cited in this rejection. The focus of Mislick, for example, is methods involving increasing or decreasing glycosaminoglycan levels in plasma or proteoglycan levels on the cell surface to impact the level of transfection of polynucleotides. To achieve increased levels of transfection, Mislick teaches increasing the amount of membrane-associated proteoglycans in the cell and decreasing plasma concentrations

of glycosaminoglycans. Thus, methods involving the administration of glycosaminoglycan analogs to facilitate viral entry, such as those of the present claims, would be inconsistent with the teachings of Mislick.

The other reference cited in this rejection, Marasco, describes the use of lentivirus vectors, such as HIV vectors, for use in gene expression studies, and nowhere suggests or provides motivation to enhance viral infectivity *in vivo* by the use of a charged compound, such as dextran sulfate.

Thus, because none of the cited references, alone or in combination, suggests or provides motivation to carry out the claimed methods, applicants respectfully request that the rejection under § 103(a) be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. Applicants also request that, if possible, the Examiner contact the undersigned by telephone in the event that the next action in this case is not a Notice of Allowance. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110-2214
Telephone: 617-428-0200
Facsimile: 617-428-7045